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Evolving research and stakeholder perspectives on pharmacogenomics

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The past decade has been a time of important change in pharmacogenomics. There is an increasingly clear understanding of the relationship between genetic variation and drug response, low-cost testing technologies are becoming available, and pharmacogenomics is playing an increasing role in drug development. Key stakeholders in the U.S. healthcare system are responding to these changes in various fashions. In this commentary, we provide a brief overview of these developments.

Academic research

Academic researchers are pursuing innovative approaches to discover novel pharmacogenomic variants, evaluating their potential clinical use, and addressing barriers to implementation in medical practice. For example, researchers are conducting collaborative genome-wide association studies (GWAS) to identify novel ‘druggable’ targets for further development by the pharmaceutical industry, and evaluating the comparative effectiveness of pharmacogenomic testing in multi-center randomized controlled trials (RCTs) for both warfarin and clopidogrel therapy. The Pharmacogenomics Research Network (PGRN) is facilitating the incorporation of pharmacogenomic information in the medical record, working with underserved populations that have not traditionally participated ingenomics research, and developing guidelines through its Clinical Pharmacogenetics Implementation Consortium (CPIC) to assist clinicians in the use of test information.[1, 2]Complementing this effort is the Electronic Medical Records and Genomics (eMERGE) network, an NIH-funded consortium that seeks to integrate clinical data from electronic medical records with genetic samples and eventually incorporate pharmacogenomic findings and genomic medicine into clinical care.[3]

Pharmaceutical industry

The pharmaceutical industry is increasingly using pharmacogenomic strategies to identify patient subgroups with improved benefit-risk profiles. For example, lumiracoxib is a cyclooxygenase II inhibitor that initially received a non-approvable letter from the FDA due

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to hepatotoxicity.[4] Novartis has discussed seeking approval for lumiracoxib in combination with a genetic test to screen for major histocompatibility complex (MHC) variants associated with liver injury. Similarly, a recent study by GlaxoSmithKline investigators has identified MHC genetic variants associated with liver damage in response to lapatinib, which is already FDA-approved for the treatment of breast cancer.[4]Pharmacogenomics of acquired (i.e., tumor) genomic variation is playing an increasing role in the efficacy of cancer drugs. The EGFR tyrosine kinase inhibitors erlotinib and gefitinib recently have been shown to be more effective in patients with non-small cell lung cancer (NSCLC) who have certain *EGFR*tumor mutations, and Pfizer is developing another drug for NSCLC, crizotinib, which is projected to be indicated for 3–5% of patients with an *EML4-ALK* fusion gene variation.[5]

Clinicians and patients

The perspectives of clinicians and patients regarding pharmacogenomics continue to evolve. A recent study reported that patients wanted information about why a pharmacogenomic test is needed and what the test results mean.[6] Healthcare professionals, on the other hand, appeared to focus on both the predictive accuracy and waiting time for a test result.[6] Several specialty professional organizations have released guidelines regarding pharmacogenomic testing. For example, the American Society of Clinical Oncology (ASCO) recommends KRAS mutation screening for patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy. By contrast the American College of Cardiology (ACC) Foundation/American Heart Association (AHA) recommends against routine genetic testing prior to clopidogrel initiation, but suggests that such testing could be considered in some high risk patients.[7–8]

Managed care organizations and benefits managers

Managed care organizations have approached reimbursement for pharmacogenomic testing on a test-by-test basis. For cases in which a clear and compelling need exists, coverage and reimbursement usually have been provided; for example for *KRAS* testing in colon cancer and gene expression profiling in early stage breast cancer. In contrast, when the clinical value has yet to be established, such as with*CYP2D6* and *CYP2C19* genotyping array, reimbursement is not available. Several large pharmacy benefits managers have taken a proactive role in providing pharmacogenomics services, and in establishing the systems and evidence base to support their use. These approaches reflect the opportunity to deploy pharmacogenomic information within existing pharmacy services infrastructures.

Federal government

The federal government plays a central role in the development, evaluation, and regulation of pharmacogenomics. In addition to the PGRN and eMERGE research networks, recent NIH funding requests have focused on the integration of whole exome sequencing information into clinical practice and a National Center for Advancing Translational Sciences (NCATS) has been proposed with the mandate most likely including development of pharmacogenomics tools to help fill the drug development pipeline.[9] Furthermore, major efforts in comparative effectiveness research (CER) undertaken as part of recent healthcare reform are directed toward translational research in cancer genomics.

Systematic evidence evaluation on pharmacogenomics has been supported by the federal government through the Agency for Healthcare Research and Quality (AHRQ), the Center for Medicare and Medicaid Services (CMS), and the CDC's National Office of Public Health Genomics, which established the genomics-focused group EGAPP.[10] EGAPP has made eight recommendations to date, including three on pharmacogenomic tests. CMS

recently issued a national coverage decision for warfarin pharmacogenomic testing, stating there is sufficient evidence to support "coverage with evidence development," a classification that pays for testing in an RCT setting.

The FDA has increased its efforts to review pharmacogenomics data submitted by drug companies and has made several notable updates to drug labels (e.g. warfarin and clopidogrel) to include pharmacogenomic information. However, the FDA does not *require* pharmacogenomic testing for any specific drugs, with the exception of testing for specific tumor mutations in cancer or viral genotypes. In addition, the FDA recently released a draft guidance on the use of genomic data in early clinical trials that emphasizes the value of collecting genetic samples from patients enrolled in studies, which may increase the use of pharmacogenomics in drug development.

Implications for clinical practice

While use of genomics to guide treatment decisions is becoming more common in oncology, relatively few tests are in use in other disease areas. Whole-exome assays likely will introduce a new approach in genomics with the potential for extremely low cost tests on a per genotype basis, and the possibility of obtaining genomic information before it is needed clinically. A critical question facing clinicians will be the evidence thresholds for using such information in practice. There are no uniform evidentiary standards for clinical implementation, but frameworks have been created by groups such as EGAPP and CPIC.[2, 10]Clinicians considering a pharmacogenomic test should consider several key questions.(Table). Most importantly, clinicians should not be early adopters of a test until a relationship has been established between the test result and drug response, and the findings have been validated in rigorously conducted studies.

Ultimately clinicians and healthcare systems will have to decide which frameworks are best suited for their needs. For example, will RCT-level data on safety and efficacy be required, as for new drugs and biologics? Or will plausible benefit based on mechanisms and indirect evidence be sufficient, as for drug-drug interactions? The answer will depend on the specifics of the gene, drug, and disease, but novel decision-making frameworks would be helpful in resolving conflicting stakeholder perspectives on this issue. In summary, clinicians should expect a challenging yet exciting period over the next five years, with a measured pace of introduction of new pharmacogenomic information and the beginning of a transition to whole-exome sequencing.

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Table

Checklist for consideration of a pharmacogenomic test

1	Is there a relationship between the test result and response to drug therapy?
2	Have the initial results been validated?
3	What is the frequency of the genomic variant in the patient population?
4	Is there a clear course of action based on the test result?
5	What are the patient outcomes - benefits and harms - of modifying drug therapy?